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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/071,541	05/04/98	HUANG H	040750-5001

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EXAMINER	
FONDA, K	
ART UNIT	PAPER NUMBER
1623	14

DATE MAILED: 06/06/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trad marks

Office Action Summary	Application No.	Applicant(s)	
	09/071,541	HUANG ET AL.	
	Examiner	Art Unit	
	Kathleen Kahler Fonda, Ph.D.	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12-18-00 & 3-13-01* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☐ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *9 & 13* .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other: .

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1-16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

Claim 1 lacks positive antecedent basis for "the resistance," "the induction," and "the increased rate", and is therefore indefinite.

Claims 8, 12, and 16 are indefinite because the phrase "its derivatives" has no particular art-recognized meaning, and has not been adequately defined in the specification.

Claims 9 and 13 lack positive antecedent basis for "the resistance", "the induction", and "the increased rate" and are therefore indefinite.

Claims 9 and 13 are furthermore indefinite because they do not state what it is that targets the recited "target cell or tissue". Applicant will note that claim 1 is not subject to this rejection because claim 1 states "a target cell or tissue of a mutant EGFR gene".

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless ⁘

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1-7 are rejected under 35 U.S.C. 102(a) as being anticipated by NAGANE *et al*. (C24). The last sentence of the reference states, "[W]e are currently testing CDDP treatment of U87MG.ΔEGFR cells in combination with tyrphostins, specific tyrosine kinase inhibitors of ΔEGFR." The statement was made during a presentation at a meeting held January 9-13, 1998, and Applicant's filing date is May 4, 1998. Thus the claims are anticipated.

Claims 1-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over HAN *et al*. (K) in view of REED (A).

Applicant claims a method of modulating inhibition of apoptosis in a target cell or tissue of a mutant EGFR gene by administering an effective amount of a tyrosine kinase inhibitor to the cell or tissue, in combination with a therapy which is effective to induce apoptosis or increase the rate of apoptosis. The mutant EGFR gene may be ΔEGFR. The cell or tissue may be a tumor selected from the group consisting of glioma, breast cancer, lung cancer, and ovarian cancer. The therapy effective to induce apoptosis or increase the rate of apoptosis may be administration of cisplatin, paclitaxel, or vincristine. The tyrosine kinase inhibitor may be tyrphostin AG1478.

Applicant also claims a pharmaceutical composition and a kit for treating cancer comprising (A) an amount of an agent which is effective to induce apoptosis or increase the rate of apoptosis in a target cell or tissue, and (B) an amount of a tyrosine kinase inhibitor effective to reduce resistance mediated by a mutant EGFR to induction of apoptosis or to increased rate of apoptosis in a target cell or tissue. The agent may be cisplatin, paclitaxel, or vincristine. The tyrosine kinase inhibitor may be tyrphostin AG1478.

HAN teaches that tyrphostin AG1478 is a tyrosine kinase inhibitor that preferentially inhibits human glioma cells expressing the mutant ΔEGFR rather than wild-type EGFR; see the abstract. Additionally, HAN suggests that because tyrphostin AG1478 is a relatively specific inhibitor of ΔEGFR, it may be therapeutically useful with regard to glioblastomas, and breast, lung, and ovarian cancers, because the ΔEGFR mutation occurs frequently in these cancers; see the abstract and the last two paragraphs on page 3861. HAN does not state that a tyrosine kinase inhibitor such as tyrphostin AG1478 should be administered together with a therapy which is effective to induce apoptosis or increase the rate of apoptosis.

REED teaches that cisplatin, taxol (also known as paclitaxel), and vincristine are known cancer chemotherapeutic agents which have in common an ability to induce apoptosis in cancer cells; see column 22, lines 4-15.

It would have been obvious for a person of ordinary skill in the art at the time of the invention to provide a method of modulating inhibition of apoptosis in a target cell or tissue of a mutant EGFR gene by administering an effective amount of a tyrosine kinase inhibitor to the cell or tissue, in combination with a therapy which is effective to induce apoptosis or increase the rate of apoptosis, wherein the mutant EGFR gene is ΔEGFR; the cell or tissue is a tumor selected from the group consisting of glioma, breast cancer, lung cancer, and ovarian cancer; the therapy effective to induce apoptosis or increase the rate of apoptosis is administration of cisplatin, paclitaxel, or vincristine; and the tyrosine kinase inhibitor is tyrphostin AG1478. An ordinarily skilled worker would have been motivated to do so in order to obtain the expected combination of therapeutic benefits with regard to cancer treatment. HAN had clearly suggested that use of tyrphostin AG1478 for treatment of glioblastomas, and breast, lung, and ovarian cancers. As taught by REED, cisplatin, taxol (also known as paclitaxel), and vincristine were known cancer chemotherapeutic agents which could induce apoptosis in cancer cells. Because tyrphostin AG1478 had been taught by HAN to be a relatively specific inhibitor of ΔEGFR, an ordinarily skilled worker would have expected the claimed combination therapy to result in modulation of the apoptosis-inhibiting effect of ΔEGFR, in accordance with the instant method claims.

It would furthermore have been obvious to provide a pharmaceutical composition or kit for treating cancer comprising (A) an amount of an agent which is effective to induce apoptosis or increase the rate of apoptosis in a target cell or tissue, and (B) an amount of a tyrosine kinase inhibitor effective to reduce resistance mediated by a mutant EGFR to induction of apoptosis or to increased rate of apoptosis in a target cell or tissue, wherein the agent is cisplatin, paclitaxel, or vincristine; and the tyrosine kinase inhibitor is tyrphostin AG1478. An ordinarily skilled worker would have been motivated to do so in order to provide a therapeutically useful composition or kit to be used in cancer treatment (see the Examiner's explanation of obviousness of the method in the previous paragraph), which would enhance compliance with an appropriate treatment regimen, as well as provide added convenience for both clinician and patient.

Applicant is reminded that it is well established that no patentable invention resides in combining old ingredients of known characteristics where the results obtained thereby are no more than the additive effects of the ingredients. See *In re Sussman*, 1943 C.D. 518; *In re Huellmantel*, 139 USPQ 496; and *In re Crockett et al.*, 1266 USPQ 186. Also, it is obvious to combine ingredients which have been separately employed for a given purpose in order to obtain the expected combination of benefits. See *In re Greenfield*, 571 F.2d. 1185, 197 USPQ 227 (CCPA 1978). In the instant case, there has been no clear and

convincing showing (see I*n re Lohr et al.*, 137 USPQ 548), commensurate in scope with the claims (see *In re Lindner*, 173 USPQ 356; *In re Hyson*, 172 USPQ 339, and *In re Boesch et al.*, 205 USPQ 215 (CCPA 1980)), of any unexpected results.

Applicant's arguments filed 12-18-00 have been fully considered but they are not persuasive.

Applicant argues that the results obtained are not merely additive, but instead are surprising and synergistic. Applicant asserts that the experimental results provided in the specification, for example Figure 6B, provide evidence of unobviousness. The Examiner does not agree. Based on the known activity of tyrphostins to inhibit tyrosine kinase activity, the result obtained does not appear to be unexpected.

Applicant argues that the prior art, in particular U.S. Patent 5,597,798 to Howell *et al.*, teaches away from doing what Applicant has done. According to Applicant, Howell teaches that increasing tyrosine kinase activity by administering EGF increases cell sensitivity to agents such as cisplatin, while Applicant teaches that decreasing tyrosine kinase activity by administration of inhibitors increases cell sensitivity to such agents. This argument is not convincing because Howell does not appear to representative of the entire state of the art at the time of the invention. For example, Gulli *et al.* (C13) had taught that a higher dosage of EGF inhibited cell proliferation, while a lower dosage increased cell proliferation. Similarly,

Levitzki (D2, page 913, second column) had stated in 1990, "If one designs blockers for the substrate domain of the protein tyrosine kinase (PTK*), it is likely to yield an effective and selective antiproliferative agent." Thus the Howell teaching, when considered in context, does not constitute a teaching away.

No claim is allowed.

Papers relating to this application may be submitted to Technology Center 1600 by facsimile transmission. The number of the fax machine for official papers in Technology Center 1600 is (703) 308-4556. Any document submitted by facsimile transmission will be considered an official communication unless the cover sheet clearly indicates that it is an informal communication.

INTERNET INFORMATION: Secure and confidential access to patent application status information is now available; see http://www.uspto.gov/ebc/index.html for more information. Also, http://www.uspto.gov/web/offices/ac/comp/fin/clonedefault.htm may be used to pay patent maintenance fees, pay non-filing application fees, and maintain USPTO deposit accounts.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Kathleen Kahler Fonda, at telephone number (703) 308-1620. Examiner Fonda can generally be reached Tuesday through Friday, and on alternating Mondays, from 7:30 a.m. until 5:00 p.m. If the

Examiner cannot be reached, questions may be addressed to Supervisory Patent Examiner Gary Geist at (703) 308-1701. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-1235.

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Art Unit 1623